Fetal Diaphragmatic Hernia: Pathophysiology, Natural History, and Outcome

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Congenital diaphragmatic hernia (CDH) is an anatomically simple defect that is easily correctable after birth by removing the herniated viscera from the chest and closing the diaphragm. However, 50–80% of all infants with CDH die of pulmonary insufficiency despite optimal postnatal care because their lungs are too hypoplastic to support extraterine life, even at term.\(^1\,\,2\) Since the pulmonary hypoplasia appears to be a developmental consequence of compression by the herniated viscera, removal of this space-occupying lesion in utero should allow pulmonary development to proceed, so that pulmonary function will be adequate to support life at birth.

Before this formidable surgical intervention is considered, the pathophysiologic rationale for correction of CDH in utero must be proved correct (i.e., that decompression will allow the fetal lung to grow and develop). In addition, prenatal diagnosis of the human fetus with CDH must be proved accurate, and the natural history of untreated human fetal CDH must be established.

We review 6 years of experimental work that supports the pathophysiologic rationale for correction of CDH in utero and present recent clinical experience with prenatal diagnosis and management that elucidates the natural history of human fetal CDH.

Fetal Lung Growth and Development

Our understanding of how human lung growth is affected by CDH has improved with recent observations on normal growth.


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490
and development of the airways and pulmonary vasculature. The bronchial tree is developed by the 16th week of gestation, at which time the full adult number of airways is established. Alveoli continue to develop even after birth, increasing in number until an individual is at least 8 years of age, and increasing in size until growth of the chest wall is completed. The growth of the blood vessels supplying the acinus (intraacinar vessels) parallels alveolar development. Fetal breathing movements are necessary for lung growth: section of the phrenic nerve in fetal lambs or absence of the phrenic nerve in the human fetus both lead to pulmonary hypoplasia.

In the fetus with CDH, the pleuroperitoneal canal fails to close by the time the intestines return to the abdomen, at 8–10 weeks of gestation. The severity of pulmonary developmental abnormalities depends on when and to what extent viscera herniate into the chest; that is, on the timing and degree of compression of the lung during development. If a large volume herniates into the chest during the stage of formation of the conducting airways (16 weeks), the number of bronchial divisions will be reduced as a result of encroachment on the thoracic volume available for lung development. Because the compression persists during the later stages of gestation, airway size is diminished, and the number and size of sacculles, alveoli, and preacinar and intraacinar vessels are decreased. There is an increase in arterial medial-wall thickness and extension of muscle peripherally into the small preacinar arteries. The effect on the ipsilateral lung is greater. Careful examination of the lungs of infants with CDH who die soon after birth confirms these expected morphologic malformations.

It is clear that the lung made hypoplastic by CDH can grow and develop after it is decompressed at birth, but the potential for further growth is limited by the relatively late timing of decompression. The crucial question is whether correction of CDH before birth will allow the compressed and underdeveloped lung to grow and develop sufficiently to improve survival rates at birth (Fig. 1). This question can only be answered experimentally.

**Experimental Pathophysiology**

**The Fetal Lamb Model**

To study the pulmonary hypoplasia that accompanies CDH and the possibility of reversing these changes by correcting the CDH in utero, we developed a model in which a conical, silicone-rubber balloon was progressively inflated in the left
hemithorax of fetal lambs over the last trimester to simulate compression by growing viscera. Lambs with inflated intrathoracic balloons, although vigorous at delivery, deteriorated rapidly, despite maximal resuscitation. Lambs with simulated CDH developed progressive hypercarbia, acidosis, and hypoxia and died of respiratory insufficiency despite maximal resuscitation and ventilatory support.

This model produced a clinical and pathologic picture strikingly similar to that seen in infants with CDH. As in the human neonate with CDH, the neonatal clinical condition appeared to be a pathophysiologic consequence of pulmonary hypoplasia. Once satisfied with the model, we could ask the crucial question: Would the compressed lung grow and develop if decompressed in utero by deflating the balloon? We found that deflation of the balloon at day 120 (simulated “correction”) allowed sufficient lung growth and development to alleviate respiratory insufficiency and to ensure survival in five of five lambs delivered by cesarean section. Lambs with simulated correction of CDH were easily resuscitated and were viable when resuscitation was discontinued after 2 hours. Because all lambs with simulated CDH died, it was apparent that simulated correction accounted for the improved survival. Simulated correction produced a significant (p < 0.01) increase in lung weight, air capacity, compliance, and area of the pulmonary vascular bed (Fig. 2). The efficacy of intrauterine correction was confirmed by three twins studies in which simulated CDH in one twin (uncorrected) was compared with simulated correction in the other. The twin with simulated CDH died, whereas the corrected twin survived. The lungs of the corrected twin were larger and more compliant and had an increased pulmonary vascular bed. These studies demonstrated that simulated correction of CDH by decompressing the thoracic balloon allowed sufficient lung growth to ensure survival at birth.

**Feasibility and Technique of Fetal Surgical Correction**

Although the balloon model established the pathophysiologic efficacy of intrauterine repair, it could not be used to study the feasibility of correction or to develop the

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**FIG. 2.** Summary of data in the fetal lamb model. Lambs with simulated CDH died, despite maximal resuscitation, and had severely hypoplastic lungs. Lambs “corrected” by balloon deflation in the middle of the last trimester had sufficient lung growth and development to permit survival at birth. Lung weight and air capacity were greater than in lambs with CDH, but less than in controls. One lamb with CDH and three corrected lambs were delivered before planned cesarean section, so viability could not be assessed. Reproduced with permission.
FIG. 3. To study the effect of increased intraabdominal and intrathoracic pressure, Silastic balloons in the fetal chest and abdomen were gradually inflated and deflated while umbilical-vein blood flow, aortic pressure, and heart rate were continuously recorded. Increased pressure markedly reduced umbilical-vein flow. Bradycardia reflected fetal distress, and compensatory tachycardia occurred when pressure was released. Blood pressure changed little and was a poor monitor of fetal condition. Reproduced with permission.¹³

surgical techniques necessary for successful surgical repair. For this purpose we had to create, and then attempt to repair surgically, actual diaphragmatic hernias. We created diaphragmatic hernias by making a hole in the left diaphragm and demonstrated that herniated viscera produced pulmonary hypoplasia comparable with that produced by the balloon. We then tried to repair the CDH surgically at a second operation.¹³

The first attempts at repair were unsuccessful. When we reduced the hernia and closed the diaphragm and abdominal wall, the first six fetuses all died in the perioperative period. To define the mechanism of fetal death, we investigated the effects of intrathoracic and intraabdominal pressure shifts secondary to returning the viscera from the chest to the abdomen. Acute studies showed that increased intraabdominal pressure secondary to volume displacement severely compromised blood flow in the umbilical vein (Fig. 3). Intrathoracic volume displacement also affects umbilical flow, probably by shifting the mediastinum and impeding venous return. Because the fetus, unlike the neonate, is totally dependent on the umbilical circulation, it cannot tolerate the pressure shifts secondary to repair of CDH. This striking physiologic difference between the fetus and the neonate must be considered in any surgical procedure on the fetal chest or abdomen.

From these experiments, it became clear that the abdominal cavity would have to be enlarged to prevent increased intraabdominal pressure after CDH repair. Leaving a skin-covered ventral hernia proved unsatisfactory, because the fetal skin was too delicate. In addition, the fascial defect might continue to enlarge with the growth of the fetus, making subsequent abdominal
wall closure difficult. Incorporating a piece of Silastic into the abdominal wall and closing skin over it proved to be a satisfactory solution. The abdominal contents were accommodated without increased pressure, and the abdominal cavity and viscera grew concurrently, thus avoiding the problem of a massive abdominal wall hernia with continued growth. To stabilize the mediastinum and minimize pressure-volume changes in the chest, the air in the partially empty left chest was replaced with warm Ringer’s lactate solution before the diaphragm was closed. Because this physiologic solution can equilibrate and be absorbed, it provides volume replacement to offset fetal “third-space” losses of surgery.

When we used these techniques (Fig. 4) for repair of the diaphragmatic hernia, 6 of 10 lambs were viable after term delivery. In autopsied lambs, the lungs were well expanded, histologically mature, and much larger than those of the controls. These studies with surgically created CDH showed that correction of diaphragmatic hernia is technically feasible when an appropriate procedure is employed. The lamb model allowed us to develop the technique and prove its safety and feasibility.

Taken together, the studies with the intrathoracic balloon and the surgically created CDH in fetal lambs demonstrated that correction of CDH in utero, with continued gestation to allow the lung to grow and develop enough to ensure survival at birth, is not only physiologically sound but also technically feasible. However, this model differs from human CDH in several respects. The human diaphragmatic defect is present much earlier in gestation—in the first trimester, although the viscera may not herniate until later. Also, although the high mortality of infants with CDH has been attributed to respiratory insufficiency secondary to pulmonary hypoplasia, the major physiologic abnormality is persistent fetal circulation. This correlates pathologically with an increase in muscle mass within the pulmonary arterioles. To answer these objections to our original model, we recently created CDH in fetal lambs very early in gestation and subsequently performed morphometric analysis of the pulmonary vascular bed.\textsuperscript{14}

**FIG. 4.** Technique for correction of CDH in utero. **A.** Surgical exposure through a stapled hysterotomy. A screw-in fetal scalp electrode monitors heart rate and variability during surgery. **B.** The herniated viscera are reduced, the air in the chest is replaced with warm Ringer’s lactate, and the diaphragm is closed with a single layer of nonabsorbable sutures. **C.** The abdomen is enlarged by Silastic abdominoplasty, and the uterus is closed with staples. Fetal operating time is less than 30 minutes. Reproduced with permission.\textsuperscript{13}
Five fetal lambs had CDH created at 60–63 days' gestation (term = 140–145 days). The CDH was repaired in two lambs at 100 days' gestation and left unrepaired in two others. All four lambs were delivered by cesarean section at term. The fifth CDH lamb was killed at 100 days' gestation to assess morphometrics at that age. Precinar arterioles were analyzed for medial muscle thickness expressed as percent external diameter (% ED) of vessel (mean ± SEM). All lung specimens were compared with control lungs from age-matched, unoperated-on lambs.

The CDH group demonstrated decreased cross-sectional area of the pulmonary vascular bed, decreased number of vessels per unit area lung, and increased muscularization of the arterial tree. Intrauterine repair of CDH at 100 days ameliorated this abnormal pulmonary arteriolar muscle hyperplasia, allowed impressive restoration of lung volume, and restored the pulmonary arterial tree toward normal.14

From these studies, we conclude that the fetal lamb model simulates the pulmonary vascular morphologic changes that correlate with fatal outcome for human neonates with CDH and persistent fetal circulation, and that fetal surgical repair of CDH ameliorates these vascular changes and permits compensatory lung growth and development.

UCSF Experience

To study the accuracy of prenatal diagnosis and define the natural history of fetal CDH, we reviewed experience with CDH at The University of California, San Francisco (UCSF) over the 3 years ending June 1982.15 All nine babies born in our institution (inborns) and six of eleven babies referred from other hospitals after birth (outborns) died, an overall mortality of 75%. Prenatal sonograms were available in all nine inborn cases. CDH was correctly diagnosed prospectively in only five cases but could be recognized retrospectively in all nine cases using the sonographic criteria developed from the study. Polyhydramnios was present in all nine cases; in seven cases, sonography was performed because the woman was large-for-dates clinically. There were no false-positive interpretations, and when necessary, the diagnosis was confirmed by amniography. In all nine cases of CDH detected in utero, the fetuses died. Seven deteriorated so rapidly that surgical repair could not even be attempted. Two who had optimal care (maternal transport, immediate resuscitation and operation) died after repair despite maximal intensive care including vaso- dilator therapy. The sonographic features of CDH derived from this clinical material have been described in detail.16 The prenatal diagnosis depends on sonographic demonstration of abdominal organs in the thorax. Although this is difficult to detect on routine sonograms, three other easily detected features—polyhydramnios, shift of the mediastinum, and absence of a normally placed stomach bubble—should prompt a more careful search for herniated abdominal organs in the fetal chest. If necessary, the diagnosis can be confirmed by amniography. Contrast material placed in the amniotic fluid and swallowed by the fetus opacifies the stomach or intestines, which are then seen in the fetal chest on plain radiograph or computed tomogram (CT) of the maternal abdomen (Fig. 5).

No false-positive diagnoses of CDH were made by ultrasound. However, it is quite possible that false-positive interpretations could arise in cases of cystic lung disease (e.g., cystic adenomatoid malformation) or with mediastinal cystic processes. In these cases, a fluid-filled structure may be present within the chest and cause a mediastinal shift. In these difficult cases, we predict that the fetal upper-abdominal anatomy would be normal and
therefore exclude a large CDH. We have been consulted about two fetuses originally thought to have CDH, who on review of sonograms had cystic adenomatoid malformations. CT or radiography, following instillation of contrast material into the amniotic cavity, further clarified the diagnostic dilemma in these two cases.

**Experience in North America:**

**Survey on Fetal CDH**

Because our initial clinical experience with fetal CDH was very discouraging (no survivors out of seven fetuses prospectively diagnosed before birth), we examined the experience at other perinatal centers by means of a survey. We hoped to define the natural history of fetal CDH and determine the pathophysiologic features that affect clinical outcome. We found 94 cases of fetal CDH from surgeons and obstetricians in North America and obtained detailed information by follow-up telephone conversations and questionnaires. 17

Prenatal diagnosis was made initially in 88 cases and retrospectively in 6 cases. In the majority of cases (66%), sonography was performed because the mother was large-for-dates because of polyhydramnios. Nineteen percent of the studies were part of a routine obstetric evaluation. Other indications were much less common. The diagnosis was made by ultrasound in 97% of cases, with confirmation by amniogram or single-section CT scan in 14 instances.

Remarkably consistent, the ultrasound findings included herniated abdominal viscera, abnormal upper-abdominal anatomy, and mediastinal shift away from the side of herniation. Polyhydramnios was present in 76% of cases. An important ultrasound finding was that herniated abdominal viscera moved in and out of the chest in several fetuses, suggesting that fetal CDH is a dynamic process.

The earliest diagnosis was made at 17
FETAL DIAPHRAGMATIC HERNIA

FIG. 6. Gestational age of fetus at time of diagnosis—61 valid responses. Survival mean = 29.0 weeks, nonsurvivor mean = 28.5 weeks, N = 61, range = 17–40 weeks. Reprinted with permission.17

weeks' gestation, and the range was 17 to 40 weeks (Fig. 6). Survivors and nonsurvivors showed no significant difference with regard to gestational age of diagnosis, the mean of which was about 29 weeks. The average gestational age at time of delivery was about 37 weeks (Fig. 7).

There were several errors in diagnosis. These included six additional cases in which CDH was misdiagnosed prenatally and proved to be cystic adenomatoid malformation in four fetuses, lung leiomyosarcoma in one fetus, and mediastinal cystic teratoma in one fetus. There were also some errors made regarding diagnosis of hernia side. In the four cases of bilateral CDH, only one side was diagnosed prenatally. Two cases of right CDH were thought to be left-sided before birth. In addition, one case of CDH was misdiagnosed prenatally as esophageal atresia with tracheoesophageal fistula.

Outcome

Ninety percent of the cases had optimal perinatal care with maternal transport, planned delivery, and immediate resuscitation. Despite sophisticated postnatal therapy, the overall outcome was disappointing (Fig. 8). Only 20% of these babies survived (19 out of 94 cases). Although most of the survivors did well, three of these infants developed severe bronchopulmonary dysplasia during prolonged postoperative respiratory support. One infant subsequently died at six months from cardiomyopathy.

There were 27 prenatal or preoperative deaths, and almost half of these were due to lethal associated anomalies. Five deaths occurred before transport, and 10 neonates deteriorated so rapidly that surgical repair could not even be attempted.

There were 46 postoperative and 2 intraoperative deaths. Many of these infants were moribund in the operating room. Seventy-four percent of the infants died during the first 24 hours postoperatively, usually secondary to the sequelae of persistent fetal circulation. Two infants treated with extracorporeal membrane oxygen-


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**FIG. 9.** Lethal associated anomalies (81 valid responses). Reprinted with permission.17

A total of 15 cases had these anomalies.

**Mortality Factors**

Sixteen percent of the fetuses in this series had lethal associated anomalies (Fig. 9). These anomalies were detected prospectively in 7 of 11 cases in which prenatal diagnostic data were available. In addition, three fetuses with right and one fetus with bilateral CDH were hydropic. Isolated, nonlethal anomalies were present in 6 cases.

An important prognostic indicator was the presence of polyhydramnios (Fig. 10). Polyhydramnios not only was common but also was a predictor of extremely poor clinical outcome—only 11% survived. The survival rate was 55% for fetuses in which polyhydramnios was not present.

With regard to management of delivery, there was a high incidence of cesarean section (Fig. 11). Often side-by-side operating rooms were set up—one for the mother's cesarean section and the other for the newborn's CDH repair. In terms of survival, however, cesarean section did not appear to have any advantage over vaginal delivery. Early delivery for extrauterine repair also did not improve overall survival—only 3 infants survived out of 17 born before 35 weeks' gestation. When cases were analyzed according to hernia side, left-sided defects were seven times more common than right-sided ones. There was no difference in survival of infants with left- or right-sided hernias. All four fetuses that had bilateral CDH died.

**Discussion**

Prenatal diagnosis permits elucidation of the important pathophysiologic features of fetal CDH. Fetal CDH appears to have a dynamic variation in the timing and amount of herniated viscera, and this probably accounts for the spectrum of severity seen postnatally. One interesting finding was that one survivor clearly had CDH present at 26 weeks' gestation, but not at 20 weeks' gestation by ultrasound. In addition, we know of three survivors not included in this series that had good-quality sonograms at 20, 26, and 38 weeks'
gestation, respectively, and CDH could not be demonstrated in any of the three sonograms. All of these findings suggest that survivors either have late gestational herniation of viscera or smaller hernias that are missed by ultrasound. Conversely, nonsurvivors tended to have large defects and may have had more viscera displaced into the chest at an earlier stage of development, with consequent severe pulmonary hypoplasia (Fig. 12).

It is important that the prenatal diagnosis of CDH not only be accurate, but also predict clinical outcome. Ultrasound may not detect small CDH in utero, but it does apparently detect those fetuses that are most severely affected. Most important, polyhydramnios is not only a good prenatal marker for the presence of fetal CDH but also a good predictor for severe cases with poor prognoses. Although there were several instances in which diaphragmatic hernias were misdiagnosed or the correct hernia side was inaccurately defined by prenatal ultrasound, it is likely that diagnostic errors can be avoided by confirming the ultrasound findings by amniography with or without computerized tomography.16

Previous reports have noted that the incidence of associated lethal anomalies with CDH varied from “rare” to 56%,17-21 and in this series the incidence was 16%. Current prenatal diagnostic techniques can detect virtually all these defects. Consequently, a thorough sonographic examination of the fetus with CDH is essential to detect the presence of other structural anomalies. Amniocentesis for karyotype analysis may also be indicated, because our review included four cases of trisomy.

The prenatal diagnosis of CDH has made it possible to define the natural history of this lesion. In the past, the wide range of mortality figures from numerous surveys of CDH related more to patterns of referral than to specific therapy.1,2 Referral centers frequently do not have an opportunity to treat high-risk outborn infants with severe pulmonary hypoplasia, simply because these neonates do not survive long enough for transport. This series demonstrates that most fetuses with detectable CDH will die, and that the outcome for the fetus with CDH and polyhydramnios is particularly poor.

The principal advantage of prenatal detection of CDH is that it allows maternal transport, planned delivery, and immediate resuscitation. In the vast majority of cases, these infants had prompt, sophisticated postnatal intervention that even included ECMO in two instances. Yet, 80% of fetuses with detectable CDH died in the neonatal period despite optimal conventional therapy. This is consistent with six previously reported cases of antenatally diagnosed CDH, in which only one infant survived.22-26 The extent of pulmonary hypoplasia at birth rather than the skill or promptness of postnatal surgical repair and intensive care appears to be the major mortality factor.

Prenatal diagnosis also makes it possible to induce preterm delivery for early decompression of the fetal thorax. However, this appears to add the problem of pulmonary immaturity to the existing problem of lung hypoplasia, and survival was not improved.

**FIG. 12.** Fetal CDH appears to be a dynamic process, and early herniation of a large volume of viscera through a large defect leads to severe lung hypoplasia and neonatal death. Reprinted with permission.17
Conclusion

Prenatal diagnosis of CDH is accurate, and current techniques can detect lethal non-pulmonary anomalies and prevent diagnostic errors. Despite optimal conventional therapy, most fetuses with detectable CDH will die in the neonatal period (80% mortality). Polyhydramnios is both a common prenatal marker for CDH (present in 76% of fetuses) and a predictor for poor clinical outcome (only 11% survived). Fetal CDH is a dynamic process—nonsurvivors have larger defects and may have more viscera displaced into the chest at an earlier stage of development. It appears that surgical intervention before birth may be necessary to improve survival of the fetus with CDH and polyhydramnios.

Prenatal diagnosis may permit surgical intervention before birth. Six years of experimental and clinical investigation suggest that prenatal repair offers great hope for the fetus with CDH. The optimal time for intervention appears to be between 22 and 28 weeks of gestation. However, prenatal intervention carries considerable risk for both fetus and mother, and we remain convinced that it should not be attempted until 1) the physiologic rationale, efficacy, and feasibility are demonstrated experimentally; 2) the prenatal diagnosis of CDH is shown to be accurate, capable of excluding other anomalies, and able to predict which fetuses have sufficiently bad prognosis to justify in utero intervention; 3) the natural history and outcome of CDH in the untreated human fetus is defined by serial observations, and 4) the safety of hysterotomy and control of preterm labor are established in the nonhuman primate. Although we have now satisfied these criteria, the repair of human fetal CDH remains a formidable challenge that should not be attempted under any but the most rigorous conditions. Diaphragmatic hernia remains the best-studied and most compelling example of a defect requiring correction before birth.

References


